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959 7590 05/11/2009

LAHIVE & COCKFIELD, LLP
FLOOR 30, SUITE 3000
ONE POST OFFICE SQUARE
BOSTON, MA 02109

EXAMINER

KIM, ALEXANDER D

ART UNIT

PAPER NUMBER

1656

DATE MAILED: 05/11/2009

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/914,451

12/20/2001

Jesper Z. Haeggstrom

PVZ-006USRCE

4167

TITLE OF INVENTION: DRUG DESIGN BASED ON THE STRUCTURE OF LTA4 HYDROLASE

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	\$755	\$0	\$0	\$755	08/11/2009

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

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B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

**Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
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INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

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959 7590 05/11/2009

LAHIVE & COCKFIELD, LLP
FLOOR 30, SUITE 3000
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BOSTON, MA 02109

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I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/914,451 12/20/2001 Jesper Z. Haeggstrom PVZ-006USRCE 4167

TITLE OF INVENTION: DRUG DESIGN BASED ON THE STRUCTURE OF LTA4 HYDROLASE

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
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nonprovisional YES \$755 \$0 \$0 \$755 08/11/2009

EXAMINER	ART UNIT	CLASS-SUBCLASS
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KIM, ALEXANDER D 1656 702-027000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

- (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, 1 _____
- (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed. 2 _____
- 3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

- ☐ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s); (Please first reapply any previously paid issue fee shown above)

- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

- ☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27. ☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,451	12/20/2001	Jesper Z. Haeggstrom	PVZ-006USRCE	4167
959	7590	05/11/2009	EXAMINER	
LAHIVE & COCKFIELD, LLP FLOOR 30, SUITE 3000 ONE POST OFFICE SQUARE BOSTON, MA 02109			KIM, ALEXANDER D	
			ART UNIT	PAPER NUMBER
			1656	
DATE MAILED: 05/11/2009				

Determination of Patent Term Extension under 35 U.S.C. 154 (b)

(application filed after June 7, 1995 but prior to May 29, 2000)

The Patent Term Extension is 0 day(s). Any patent to issue from the above-identified application will include an indication of the 0 day extension on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Extension is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Notice of Allowability	Application No.	Applicant(s)	
	09/914,451	HAEGGSTROM ET AL.	
	Examiner	Art Unit	
	ALEXANDER D. KIM	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 04/02/2009.
2. ☒ The allowed claim(s) is/are 60,61,68,70,71,76 and 78.
3. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) ☒ All b) ☐ Some* c) ☐ None of the:
 1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).
 - * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
 - (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
 - 1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
 - (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

- | | |
|---|---|
| <ol style="list-style-type: none"> 1. <input type="checkbox"/> Notice of References Cited (PTO-892) 2. <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) 3. <input type="checkbox"/> Information Disclosure Statements (PTO/SB/08),
Paper No./Mail Date _____ 4. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit
of Biological Material | <ol style="list-style-type: none"> 5. <input type="checkbox"/> Notice of Informal Patent Application 6. <input type="checkbox"/> Interview Summary (PTO-413),
Paper No./Mail Date _____. 7. <input checked="" type="checkbox"/> Examiner's Amendment/Comment 8. <input checked="" type="checkbox"/> Examiner's Statement of Reasons for Allowance 9. <input type="checkbox"/> Other _____. |
|---|---|

DETAILED ACTION

Application Status

1. In response to the previous Office action, an advisory action (mailed on 03/04/2009), Applicants filed a response and amendment received on 04/02/2009.

Said amendment cancelled Claims 1-59, 62-67, 69, 72-75, 77 and 80-86 and amended Claims 60, 70 and 78. Claims 60-61, 68, 70-71, 76 and 78-79 are pending.

Examiner's amendment to the Claims

2. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment shown below was given in a telephone interview with Maneesh Gulati on 30 April 2009.

Amend the claims filed on 04/02/2009 with the following claims.

60. A method of identifying compounds that bind to a leukotriene A₄ (LTA₄) hydrolase comprising the amino acid sequence of SEQ ID NO: 1, the method comprising the steps of:

(a) crystallizing a purified LTA₄ hydrolase in the presence of bestatin to form a co-crystal of LTA₄ hydrolase and bestatin, wherein crystallization is performed by liquid-liquid diffusion in a capillary using equal volumes of a buffer:

enzyme solution consisting of:

- i) a buffer solution consisting of 28% PEG8000, 0.1 M Na-acetate, 0.1 M imidazole at a pH of 6.8 and with 5 mM YbCl₃ as an additive; and
- ii) an enzyme solution consisting of 5 mg/ml LTA₄ hydrolase comprising the amino acid sequence of SEQ ID NO:1 in 10 mM Tris-HCl at a pH of 8, supplemented with 1 mM bestatin;

wherein the crystallization results in a LTA₄ hydrolase crystal having the space group P2₁2₁2 and the unit cell dimensions a=67.59 Å, b=133.51 Å, and c=83.40 Å and wherein $\alpha=\beta=\gamma=90^\circ$;

(b) determining the atomic coordinates of LTA₄ hydrolase from the co-crystal obtained in step (a); and

(c) screening the atomic coordinates of a set of candidate compounds against the atomic coordinates obtained in step (b) to identify compounds that bind to the LTA₄ hydrolase.

61. The method of claim 60, wherein the LTA₄ hydrolase is purified by adsorption chromatography on hydroxyapatite and anion-exchange chromatography.

68. The method of claim 60, wherein the atomic coordinates obtained in step (b) correspond to the atomic coordinates defining atom 1 to atom 4876 as set forth in Table 9.

70. A method of identifying an inhibitor of LTA₄ hydrolase comprising the amino acid sequence of SEQ ID NO:1, the method comprising the steps of:

(a) crystallizing a purified LTA₄ hydrolase in the presence of bestatin to form a co-crystal of LTA₄ hydrolase and bestatin and thereafter determining its three-dimensional structure, wherein the crystallization is performed by liquid-liquid diffusion in a capillary using equal volumes of a buffer: enzyme solution consisting of:

- i) a buffer solution consisting of 28% PEG8000, 0.1 M Na-acetate, 0.1 M imidazole at a pH of 6.8 and with 5 mM YbCl₃ as an additive; and
- ii) an enzyme solution consisting of 5 mg/ml LTA₄ hydrolase comprising the amino acid sequence of SEQ ID NO:1 in 10 mM Tris-HCl at a pH of 8, supplemented with 1 mM bestatin; wherein the crystallization results in a LTA₄ hydrolase crystal having the space group P2₁2₁2 and the unit cell dimensions $a=67.59 \text{ \AA}$, $b=133.51 \text{ \AA}$, and $c=83.40 \text{ \AA}$ and wherein $\alpha=\beta=\gamma=90^\circ$; and
- iii) determining the atomic coordinates of the LTA₄ hydrolase from the co-crystal;

(b) identifying at least one potential inhibitor that is at least in part complementary to the LTA₄ hydrolase by the use of the atomic coordinates of the LTA₄ hydrolase crystal;

(c) soaking a co-crystallized LTA₄ hydrolase as obtained in step (a) with a solution of the potential inhibitor identified in step (b) to obtain a complex of the crystal of said LTA₄ hydrolase and said potential inhibitor; and

(d) determining the atomic coordinates of the crystal complex of LTA₄

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hydrolase and said potential inhibitor in step (c) to determine the structure thereof, thereby identifying the potential inhibitor as an inhibitor of LTA₄ hydrolase.

71. The method of claim 70, wherein the LTA₄ hydrolase is purified by adsorption chromatography on hydroxyapatite and anion-exchange chromatography.

76. The method of claim 70, wherein the atomic coordinates obtained in step (a) correspond to the atomic coordinates defining atom 1 to atom 4876 as set forth in Table 9.

78. The method of claim 70, further comprising the step of refining the structure of the potential inhibitor obtained in step (d) via computer modeling using this refined data and repeating steps (b)-(d).

79. Cancelled.

Statement of Reasons for Allowance

3. Claims 60-61, 68, 70-71, 76 and 78 are allowed. The following is an examiner's statement of reasons for allowance:

The instant invention is drawn to a method of identifying compounds (or inhibitor) that bind to a leukotriene A₄ (LTA₄) hydrolase comprising the amino acid sequence of SEQ ID NO: 1 (i.e., a zinc metallo peptidase, a human LTA₄), the method steps comprise crystallizing the LTA₄ hydrolase, determining the atomic coordinates of the LTA₄ hydrolase and screening the atomic coordinate of candidate compounds against the atomic coordinates of the LTA₄ hydrolase. The claimed method step of crystallizing the leukotriene A₄ (LTA₄) hydrolase in the presence of bestatin comprising the amino acid sequence of SEQ ID NO: 1; having the space group P2₁2₁2 and the unit cell dimensions a=67.59 Å, b=133.51 Å, and c=83.40 Å and wherein $\alpha=\beta=\gamma=90^\circ$; and screening the compound(s) by the coordinates determined therefrom is novel and non-obvious for one skilled in the art. The LTA₄ hydrolase inhibitor via the three-dimensional structural data obtained by the claimed method can be useful for identifying and/or making an inhibitors which may be useful in anti-inflammatory drugs, for example. A method of identifying and/or screening compound (or potential inhibitor) *in silico* using the three-dimensional structural coordinates of an enzyme and the compound is well known to one skilled in the art; wherein the compound(s) can be any molecule including previously known molecules or those which can be designed *ab initio* (or even a highbred of the two), for example; thus, the instant methods are interpreted to encompass identifying and designing various compounds from a variety of sources and means.

In view of the examiner's amendment, all outstanding objections are withdrawn.

Any comments considered necessary by applicant must be submitted no later

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than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance.

Conclusion

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEXANDER D. KIM whose telephone number is (571)272-5266. The examiner can normally be reached on 10AM-6:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alexander D Kim/
Examiner, Art Unit 1656

/SUZANNE M. NOAKES/
Primary Examiner, Art Unit 1656